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Case Report

Denosumab for Breast Cancer with Bone Metastases-Induced Hypercalcemia Complicated with Acute Renal Failure

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Abstract.

Cancer-related hypercalcemia is a relative common complication from breast cancer with bone metastasis and may cause renal failure and coma in severe condition. The cornerstone of treatment is vigorous hydration, intravenous bisphosphonates, and loop diuretic agent only after corrected hypovolemia. Bisphosphonates is related deterioration of renal function and is controversial when administered in cancer-related hypercalcemia complicated markedly renal deterioration. The receptor activator of nuclear factor-kappa Bligand (RANK-L) is an essential signal to stimulate differentiation, activity and survival of osteoclast. Denosumab, a fully human antibody which neutrolizes RANK-L leading to the loss of osteoclasts from bone surface and inhibition of bone resorption. Here, we present a case report of breast cancer-related hypercalcemia complicated renal failure was successfully treated by denosumab.

Keywords **:** breast cancer, denosumab, hypercalcemia

病例報告

以 Denosumab 治療骨轉移乳癌患者合併腎衰竭之高血鈣

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中文摘要

癌症相關高血鈣在乳癌合併骨轉移患者是個比較常見的併發症，嚴重者可能導致腎衰竭及意識昏迷。治療的黃金準則為充足水份補充、靜脈注射雙磷酸鹽藥物以及在確定低血容已矯正恢復後可以給予亨利氏環利尿劑。雙磷酸鹽藥物因有使腎功能變差之可能性，是否可用來治療癌症相關高血鈣併發嚴重腎功能損傷之患者，仍有爭議。細胞核因子 Kappa B 受體活化因子之配體(RANK-L)是促使蝕骨細胞分化、具有活性以及存活的一個必需訊息傳遞訊號。Denosumab 為一全人類成份的抗體，可以中和掉 RANK-L 而使骨頭表面的蝕骨細胞喪失，進而抑制骨頭的再吸收。我們在此報告一個以 denosumab 治療乳癌相關高血鈣併發腎衰竭成功的患者。

關鍵字: 乳癌、denosumab、高血鈣

INTRODUCTION

Hypercalemia has been reported to occur in up to 5 to 30 percent of patients with cancer during the course of their disease [1,2]. The most common cancers-inducing hypercalcemia are lung and breast cancers and multiple myeloma [2]. Hypercalcemia leads to a variety of symptoms in patients, which can range from confusion and polyuria to coma and death. The cornerstone of treatment is vigorous hydration, intravenous bisphosphonates, and loop diuretic agent only after corrected hypovolemia.

Bisphosphates, such as zolendronic acid and palmidronate, are effective therapeutic agents for hypercalcemia [3]. However, in hypercalcemia complicated with marked acute renal insufficiency, especially when serum creatinine is above 4.5 mg/dl, the usage of bisphosphanate sould be delayed [4]. Vigorous hydration, loop diuretics, and calcitonin may be applied to lower the level of serum calcium. If renal function improves, bisphsphanate should be prescribed and may be followed by definite anti-cancer therapy which can be used to control the calcium level. Denosumab is a fully human antibody which neutralizes the receptor activator of nuclear factor-kappa Bligand (RANK-L) leading to the loss of osteoclasts from bone surface and inhibition of bone resorption. The benefits of denosumab for prevention of skeletal-related event of cancer with bony metastasis have been confirmed by recent large clinical trials [5-7]. Denosumab may have a more potent effect of bone resorption inhibition than zoledronic acid by improved skeletal-related events and more adverse events of hypocalcemia in the treatment of advanced breast cancer, castration-resistant prostate cancer and other advanced cancer with bone metastases [5-7]. Here, we report a case of hypercalcemia induced by advanced breast cancer with bone metastases and complicated with marked renal injury, successfully treated by denosumab.

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CASE REPORT

A 40 year-old women was admitted to our hospital because of a left breast lump with pain for one year. Physical examination revealed a huge left breast mass with ulceration and enlarged nodes in the left axillary and periclavicular area. The biopsy of left breast tumor disclosed invasive ductal carcinoma with positive ER (80%), PR (80%) and negative HER-2/neu. CT scans of the chest and abdomen revealed a huge left breast mass with skin invasion, axillary and neck lymphoadenopathy, multiple liver and bony metastases involving the right femoral head, right acetabulum, both pubic bones, right iliac bone and vetebral bodies from T10 to L4. Advanced breast cancer with multiple metastases was diagnosed. Marked hypercalcemia and renal failure were noted. The albumin-corrected serum calcium level was 16.74 mg/dL. The serum BUN and creatinine levels were 63 and 3.57 mg/dL respectively with estimated glomerular filtration rate 15 ml/min/ $1.73m^2$. The serum parathyroid hormone and vitamin D3 were showen to be within the normal range, and cancer-induced hypercalcemia (CIH) was considered. Aggressive intravenous hydration was given initially and serum calcium and renal function declined slightly. Due to the markedly deteriorated renal function, denosumab with one single dose of 120 mg was administered subcutaneously. The following sequential data showed that the serum calcium level decreased to normal accompanied by gradually recovered renal failure (Figure 1) and then chemotherapy was administered. The serum calcium level was still in the normal range 22 days after denosumab injection.

DISCUSSION

Cancer-induced hypercalcemia (CIH) developed in

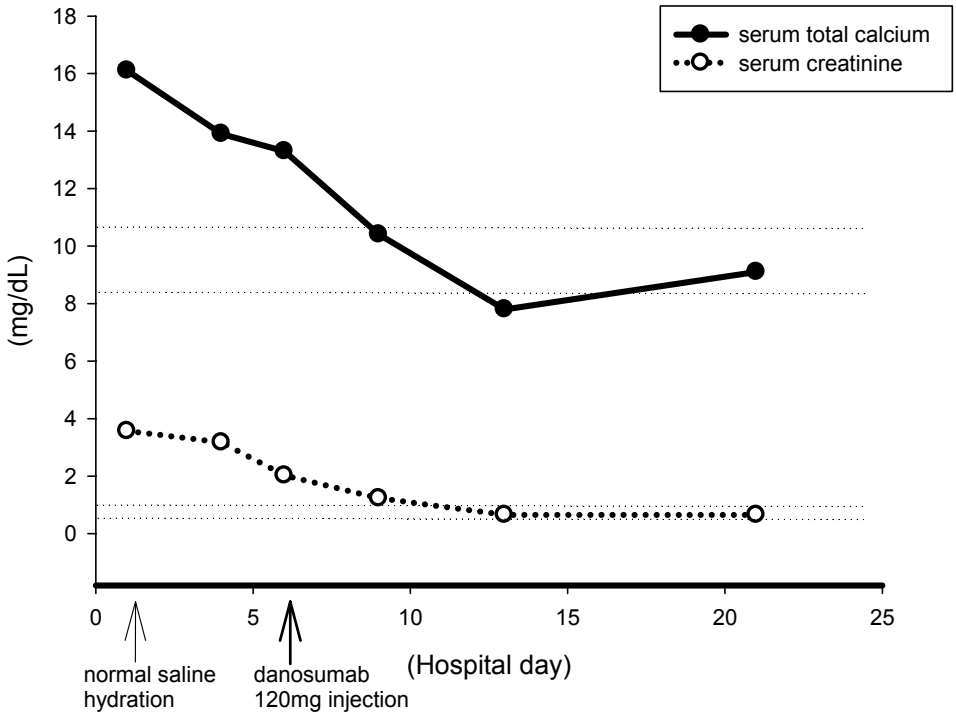

Figure 1. Time course of total serum calcium and serum creatinine levels in response to vigorous hydration and a single dose of denosumab administered (normal range of serum total calcium: 8.4~10.6 mg/dL, creatinine: 0.5~1.2 mg/dL)

5 to 30 percent of patients with cancer, and breast cancer is one of the most common cancers associated with CIH. The mechanisms of CIH include secreting parathyroid hormone related protein (PTHrP) in 80% of patients, focal osteolytic bone destruction in 20% and other calciotropic hormones (<1%), including vitamin D3 and ectopic PTH. Osteoclastic bone resorption can be induced by the any of the three mechanisms and calcium releases from the bone matrix [1,2]. Standard treatment of CIH comprises vigorous hydration, intravenous bisphosphonates (BPs), and loop diuretics only after corrected hypovolemia. However, bisphosphonates are excreted intact primarily via the kidney and have a risk to deteriorate renal function. Higher serum concentration as well as greater adverse events of deterioration of renal function are noted when administered in patients with initially impaired renal function [3]. In patients of malignancy with bone metastasis, dose adjustment for zoledronic acid is needed if renal insufficiency is mild to moderate (creatinine clearance between 30 to 60 ml/min per 1.73 m^2) but administration of bisphosphates is discouraged if creatinine clearance is below 30 ml/min per 1.73 m^2 [2,5-7]. In patients with hypercalcemia, a malignancy with severe renal impairment should be considered only after evaluating the benefits and risk of treatment. In the clinical trial, patients with serum creatinine above 4.5 mg/dL were excluded [4]. In the study of Major et al, a pooled analysis of two randomized trials comparing zoledronic acid and pamidronate in the treatment of hypercalcemia due to a malignancy included patients whose serum creatinine levels were less than 4.5 md/dL. The result showed that the complete remission rates of hypercalcemia in the zoledronic acid group and the pamidronate group were 86.7% and 69.7% (p =0.015), respectively. However, the rates of grade 3 or 4 renal toxicity were still high (2.3~5.2% in the zoledronic acid group and

4.0% in the pamidronate group) [4].

The receptor activator of nuclear factor-kappa Bligand (RANK-L) is an essential signal to stimulate differentiation, activity and survival of osteoclast. Denosumab, a fully human antibody, neutralizes RANK-L leading to the loss of osteoclasts from bone surface and inhition of bone resorption [8]. In the phase III trial of bone metastases in patients with advanced breast cancer, 1901 patients were randomly assigned to receive denosumab or zoledronic acid for prevention of skeletal-related events. The results demonstrated a more prolonged median time to the first on-study skeletal-related event (26.4 months in the zoledronic acid group, but the time has not yet been reached in the denosumab group, the hazard ratio being 0.82, p = 0.01). A greater reduction in bone turnover marker in the denosumab group (p< 0.0001) was found also. In the issue of adverse effects, there are more hypocalemia events in the denosumab group (5.5% vs. 3.4%) and less renal failure events in the denosumab group (0.2% vs. 2.5%) [7]. These results showed that denosumab was more effective and had less renal toxicity than bisphosphonates. Denosumab is a monoclonal antibody and metabolized by peptidases and cleared by the reticuloendothelial system, and probably dose not exert nephrotoxic effects [9]. The American Society of Clinical Oncology executive summary of the clinical practice guideline on the role of bone-modifying agents in metastatic breast cancer published in 2011 suggested 1) dose adjustment of bisphosphates when baseline serum creatinine clearance is ≥ 30 and < 60 mL/min, 2) patients with creatinine clearance < 30 mL/min or on dialysis may be treated with denosumab, with close monitoring for hypocalcemia is recommended [10]. However, despite the reduced dose of zoledronic acid in patients with cancer whose creatinine clearance was less than 60 mL/min per 1.73 m^2, deterioration of renal function (all grades) was observed in 20 to 21.6% of patients treated with bisphosphonates. Compared with denosumab, it occurred only in 5.9 to 11.3% of those treated with denosumab [5,7].

Denosumab for treatment of cancer induced hypercalemia is still not approved by FDA due to the lack of large and randomized studies. One phase 2 clinical trials which used denosumab for bisphosphate-refractory hypercalcemia induced by a malignancy was published in June, 2014. There were 33 patients with bisphosphate-refractory hypercalcemia due to the malignancy who received subcutaneous denosumab 120 mg on days 1, 8, 15 and 29, and every 4 weeks thereafter. The response rate after 10 days was 64% (calculated serum calcium ≤ 11.5 mg/dL and the complete response rate during the study was also 64% (calculated calcium ≤ 10.8 mg/dL). Besides, no renal toxicity was observedin patients with an impaired renal function response to denosumab therapy [11]. Another study of case series presented 7 patients of cancer-related hypercalcemia who received denosumab treatment. All but one have received bisphosphate therapy. Two patients received a single dose of denosumab 60 mg and the other five received 120 mg. Five patients achieved normalized calcium levels within 17 h after denosumab administration [12].

In Taiwan, the costs are similar between 120 mg of denosumab and 4 mg of zoledronic acid. The payment is NT 12,703 dollars for denosumab and NT 12,384 for zoledronic acid by Taiwan National Health Insurance. However, denosumab is deemed to be more effective for reducing skeletal-related events.

Denosumab is an effective therapy for cancer-induced hypercalcemia and should be considered a safe treatment for patient complicated with severe renal insufficiency. In our case and previous case series studies, a single dose of denosumab (120 mg) seems to be effective initially for hypercalcemia of malignancy and frequently repeated dose can be reserved for refractory hypercalcemia.

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